REMARKS/ARGUMENTS

Applicant thanks the Examiner for conducting an interview on January 14, 2009 at which the outstanding office action was discussed. Applicant agrees with the Examiner's summary of the interview.

The claims have not been amended but are reproduced above for ease of reference.

The paragraph numbering of the office action is used in responding to the Examiner's comments.

¶¶5-7. Applicant reiterates willingness to provide a terminal disclaimer should the claims be found otherwise allowable.

¶8. Claims 1, 2, 4, 10-12, 22-24, 31, 32, 36, 82-84, 88-90, 95-99, 101, 103, and 104 stand rejected as allegedly obvious over Becker in view of Kuby, Adair and Janeway. The Examiner alleges that it would have been obvious to select a human IgG1 isotype either for higher binding affinity as allegedly taught by Adair and Kuby or diffusability into vascular tissue as taught by Janeway.

Applicant initially notes that an alternative rejection based on Becker, Walker, Hanan and Majocha has been withdrawn. The theory underlying the rejection was that because the mouse 10D5 antibody is reported to have mouse IgG1 isotype, it would be obvious to make a human, humanized or chimeric antibody with the human equivalent of this isotype, namely, human IgG1. However, as pointed out by applicant, the closest human equivalent of mouse IgG1 is not human IgG1. This point is elaborated in an attached declaration by Dr. Shyra Gardai, an immunologist whose responsibilities include testing antibodies with different isotypes. Dr. Gardai explains that if she was selecting an isotype in a humanized antibody so the humanized antibody behaved most similar to a mouse IgG1 antibody from which it was derived, she would select a human IgG2 or IgG4 isotype (at paragraph (5)). Although the rejection has appropriately been withdrawn, the fact that its logic taught away from the claimed invention

should not be forgotten. A reference teaching away from an invention is strong evidence of non-obviousness, in fact, the very antithesis of obviousness, to which a rebuttal should not even be required. *In re Buehler*, 185 USPQ 781 (CCPA 1975); *In re Hedges*, USPQ 685, 687 (Fed. Cir. 1986).

The newly cited Janeway reference does not provide a reason specifically to select a human IgG1 isotype. The reference indicates that the property of diffusing easily out of the blood into tissue applies to IgG, IgA and IgE antibodies (p. 8. 18, last paragraph) and does not distinguish between IgG1 and other human IgG isotypes in this regard.

Applicant reiterates that the Examiner's alternate theory that human IgG1 isotype has a higher affinity than other human isotypes is a speculative overgeneralization of a single example in which an IgG1 antibody was reported to have higher avidity (not affinity) than IgG4 (Adair at p. 50, lines 9-14). Avidity is by definition a summation of affinities that may arise if an antigen is able to form multivalent bonds with an antibody. Although Janeway and other references cited by applicant (Paul, Hussain and Clark, cited as cited nos. 653, 1092, and 1091 by the supplemental IDSs filed April 16, 2007 and August 7, 2008, respectively) discuss several functional properties of antibodies that vary between isotypes, none of these articles mentions antibody binding strength as such a property. If Adair had established a general rule recognized in the art that human IgG1 antibodies have higher binding strengths than other human isotypes, one would expect that the general rule would be mentioned in articles reviewing such general properties. As the Examiner notes, Janeway (and the other cited articles) indicate that isotypes have some different properties not dependent on the particular antigen bound. However, none of these several references indicates that binding strength is such a property. The existence of any general rule that human IgG1 antibodies have highest binding strength is also disproved by the references previously recited showing that antibodies of different isotypes have about the same affinity. The simple fact that the experiments were performed and no surprise was expressed that different isotypes had about the same affinity shows that those in the field were not aware of a general rule established by Adair that human IgG1 isotype has higher binding strength than other isotypes.

Further evidence against there being a general rule that human IgG1 isotypes have highest binding strength is provided by the Gardai declaration. Dr. Gardai explains that although there are examples in which one human isotype has higher binding strength than another, there is no general rule that human IgG1 has the highest binding strength (at paragraph (3)). Dr. Gardai cites an example in which human IgG4 had the highest binding strength. Dr. Gardai concludes that unless a meaningful difference in binding strength between isotypes were experimentally demonstrated, it would not be as significant factor in her choice of isotype for a humanized antibody (at paragraph (4)).

Furthermore, as discussed in the *Washington Post* article excerpted in the last response (cited as cite no. 841 by the supplemental IDS filed April 16, 2007), concern that Alzheimer's disease was at least in part mediated by inflammation would have tended to teach away from the use of human IgG1 in that this isotype has the strongest interaction with phagocytic cells and complement.

When considered in the aggregate, the art did not provide a reason to select human IgG1 isotype for use in the claimed methods.

The Examiner continues to hold the view that there was nothing surprising about the claimed invention notwithstanding expressions of surprise and amazement by numerous independent third parties because the claimed methods are allegedly merely following Becker and Becker must be presumed to be enabling according to MPEP § 2121 notwithstanding any lack of data. In characterizing applicant's position as an argument that Becker lacks enablement, the Examiner is addressing an argument that was not made.

To reiterate applicant's position from the last response and the interview, whether the cited art provided a reasonable expectation of success is a different issue than whether the cited art references are themselves enabling. Predictability of the art is only one of eight factors used in a *Wands* analysis of enablement. It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the factors while ignoring one or more of the others. MPEP 2164.01(a). As a corollary, enablement does not necessarily imply predictability. A prophetic reference describing a proposed method can work exactly as described (i.e., be enabling) but also be unpredictable because of the nature of the subject matter (which the

Examiner acknowledges was within a difficult field in the 1990's) and because no data are provided to show that the method works. The unpredictability of Becker's proposals is evident from comments such as the following: "It's wild and amazing....Almost all scientists would have dismissed the immunization approach... because of the dogma that the so-called blood-brain barrier keeps circulating antibodies out of the brain." (*See* Sangram S. Sisodia excerpt from last response). A reference that is itself unpredictable, such as Becker, does not render future developments in the field any more predictable unless and until the source of unpredictability is removed. Thus, applicant's remarks concerning the lack of reasonable expectation of success do not require the Examiner to find a prophetic reference such as Becker to lack enablement, but simply to consider what predictive value such a reference would have had to the skilled person at the effective filing date of the application without any supportive data.

The excerpts of surprise and amazement show disinterested observers in the field were not convinced of immunotherapy as a viable treatment of Alzheimer's disease until publication of the first results showing disease modification in an animal model. Thus, a reference lacking such results would not have been viewed as being reasonably predictive of success. Such a conclusion is also consistent with the Becker application having been abandoned in all jurisdictions (*See* cite no. 1150 cited in the supplemental IDS filed on March 4, 2009). Lack of a commercial success of a reference is one factor that weakens a case of obviousness. Van der Lely v. Maschio, 222 USPQ 399 (S.D. Ohio 1984), affirmed, 748 F.2d 1568, 1984 (Fed. Cir. 1984)

Instead of considering Becker from the perspective of the skilled person not knowing whether the methods discussed in the reference would be successful in treatment of Alzheimer's disease, the Examiner appears to be viewing the reference from an artificial perspective in which it is presumed that the methods had worked and all unpredictability is removed. Accordingly, the case of obviousness requires the implausible conclusion that all the disinterested experts in the field quoted in the last response are somehow mistaken.

The source of this presumption is MPEP § 2121, which provides that "when the reference relied on expressly anticipates or makes obvious *all of the elements of the claimed invention,* the reference is presumed to be operable (emphasis supplied)." Such a presumption is

inapplicable here because Becker is not cited as disclosing or rendering obvious all elements of the invention and more fundamentally because it is not the operability of Becker that has been put at issue here. Operability, which equates to enablement, is not the same as predictability for the reasons discussed above.

The Examiner also alleges that the comments of surprise from third parties do not relate to the human IgG1 feature of the present claims. In fact, some of the comments do relate indirectly to this feature. The *Washington Post* article excerpted in the last response commented that "The idea was revolutionary because most Alzheimer's experts believe that the inflammation provoked by amyloid plaques contributes to the destruction of brain cells. Many predicted that stirring up the immune system with a vaccine would only make the disease worse." The human IgG1 isotype has the strongest interaction with phagocytic cells and complement and thus would tend to stir up the immune system the most. The surprise expressed at the concept that stirring up the immune system would be beneficial rather than provoking an undesired inflammatory response would have applied all the more to the selection of a human IgG1 isotype.

Having considered the various rationales for combining the references and unpredictability of the art, applicant returns to the *KSR* case. Assuming the Examiner is correct that the *KSR* case and the present case have in common that a combination of references discloses the elements of the claimed invention, the similarity ends there. Such is insufficient for obviousness. Inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known. A patent composed of several elements is not proved to be obvious merely by demonstrating that each of its elements was independently known in the prior art. (*KSR*, 82 USPQ2d at 1396). Becker's discussion of antibodies is far removed from that of a foot peddle or sensor of *KSR*. Whereas both an adjustable foot peddle and electronic sensor were in commercial use in the *KSR* case, Becker does not provide even an example of an antibody, much less experimental evidence that the antibody could be used. Although the Examiner treats Becker as being no less predictable than such well-known commercial devices, this treatment arises from an artificial presumption inapplicable here to the disregard of the objective evidence provided by disinterested third parties and the abandonment of the Becker application by its

owners. Likewise, the effect of different isotypes in treatment of Alzheimer's disease could not been predicted in similar fashion to the role of a foot peddle or sensor in a car. The *Washington Post* article excerpted above, expressing concern that Alzheimer's disease was at least in part mediated by inflammation would have tended to teach away from the use of human IgG1 as would the Examiner's now discarded theory that the artisan would have sought to select the humane isotype closest in properties to mouse IgG1. The other theories of diffusability or higher affinity are not specific to IgG1 or speculative but in any event are proposed in isolation without balancing against forces teaching away from the selection of human IgG1.

In sum, the present claims are distinguished from *KSR* in the nature of what is being combined and particularly in the predictability or lack of thereof of the combination.

Applicants acknowledge the Examiner's comments that all determinations of obviousness are necessarily based on hindsight and he has attempted to weigh all of the evidence and avoid improper hindsight. Unfortunately, improper hindsight can arise unconsciously. For example, a recent review article providing empirical evidence of the pervasive influence of improper hindsight in obvious determinations comments:

> [O]nce outcome information is known, people are cognitively incapable of preventing that information from influencing their understanding of past events. As a result, individuals consistently (and unconsciously) exaggerate what could have been anticipated in foresight and not only tend to view what occurred as having been inevitable, but also as having appeared relatively inevitable.
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> Mandel, Yale Journal of Law & Technology, Vol. 9, No. 1, 2007 at p. 3.

Here, there are several objective indicators that improper hindsight may have unconsciously entered the obviousness assessment. First, the obviousness rejection is not based on a realistic assessment of the state of the art at the time of the invention but on an artificial presumption in which predictability of treating Alzheimer's disease is assumed. Second, the case of obviousness does not flow directly from the cited references but on an overgeneralization or overstatement of their alleged teaching. No general statement as to the higher affinity of human IgG1 or higher diffusability of human IgG1 relative to other isotypes is present in the cited art. Third, the alleged rationales for combining the references disregards evidence teaching away

from the claimed invention. Given an artificial assessment of predictability, an overstatement of the teaching of some of the art, and neglect of art teaching away from the claimed invention, the claimed invention might appear to have been relatively inevitable. Given a realistic assessment of the unpredictable and difficult nature of the art, a closer adherence to what the references actually say, and appropriate taking into account of evidence inconsistent with the proposed theory of obviousness, applicant submits that obviousness would not have been apparent.

As to claims 103 and 104, the Examiner asserts that although he is unable to determine whether these claims would have been obvious he includes them in the rejection anyway under MPEP § 2112(l) because the additional limitations of claims 103 and 104 are functional. In reply, MPEP §2112 IV still requires that the Examiner provide a rationale or evidence tending to show inherency. The Examiner has provided no reasoning to explain how an antibody that specifically binds Aβ in beta-sheet form *without* binding in alpha helical form or vice versa (as discussed) by Becker necessarily binds Aβ in *both* aggregated and dissociated forms as specified in claims 103 and 104. Furthermore, a description of an antibody binding specificity cannot be dismissed merely as being a functional property, it being well understood in the art that differences in binding specificity reflect underlying differences in structure. In the alternative, the Examiner alleges Becker discloses antibodies binding to Aβ generically. Applicant is unable to find such disclosure particularly in the context of therapeutic methods and requests clarification from the Examiner where such disclosure is present.

¶¶9-18. All of the remaining art rejections are also premised on the allegation that the combination of Kuby, Janeway and Adair would have rendered obvious the selection of a human IgG1 isotype in the claimed methods. The distinctions discussed above are thus equally applicable.

¶19. Claims 82, 83, 85, 86, 89, 90, 97-100 and 104 stand rejected for alleged obviousness type double patenting over claims 1 and 3-17 of US 6,710,226. Reconsideration is respectfully requested because the screening method claims of the '226 patent (Groups V and VI, subsequently pursued together) were deemed to be a separate invention from the method of

treatment claims (Group I) of the current case by a restriction requirement of September 29, 2000 in the current case.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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